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# The Growth of Nerve Circuits

*Recent studies of the process of nerve repair have led to a new theory of how the complex networks and pathways of the central nervous system are formed in the embryo*

by R. W. Sperry

Severe damage to the principal motor nerve of the face may leave a person afflicted with a condition known as "crocodile tears." As the injured nerve regenerates, fibers that originally activated a salivary gland can go astray and connect themselves to the lachrymal gland of one eye. Thereafter every situation calling for salivation induces weeping from that eye. Often the regenerating salivary fibers invade sweat glands and related organs in the skin, causing profuse sweating and flushing in areas of the face and temple. The random shuffling of motor-nerve connections to the muscles of the face characteristically deranges facial expression, causing a grimace-like contraction of the affected side. Sometimes, to prevent atrophy of the facial muscles when the injured facial nerve fails to regenerate, surgeons will connect the denervated facial muscles to a nearby healthy nerve: the motor nerve of the tongue or the motor nerve of the shoulder muscle. The restored facial movements still lack meaningful expression and tend to be associated with the chewing movements of the tongue or the action of the shoulder muscles.

Naturally the primary concern of the patient in such cases is whether or not normal function can be restored. If the symptoms do not clear up spontaneously, can they be corrected by training and re-education? By faithful practice in front of a mirror, for example, can a patient learn to inhibit the crocodile tears and regain control of facial expression?

Not so long ago the reply to such questions was a confident "Yes." For most of the present century investigators and physicians were agreed that the central nervous system is plastic enough so that any muscle nerve might be reconnected to any other muscle with good functional success. Sensory-nerve fibers were thought to be equally interchangeable within a given sensory system. It was believed that the central pathways in the nervous system were first laid down in the embryo in randomized equipotential networks. By use and learning these pathways became channelized; connections that proved adaptive in function were reinforced, while the nonadaptive ones underwent "disuse atrophy." Learning thus determined not only the function but also the structure of the nervous system. This theoretical picture was sustained by experiments on animals in which, according to the literature, the crossing of major nerve-trunks was followed by full restoration of function. In the prevailing mood of optimism physicians were able to report encouraging progress by their patients.

During the past 15 years, however, scientific and medical opinion has undergone a major shift, amounting to an almost complete about-face. No longer do physicians encourage the patient with a regenerated facial nerve to try to regain control of facial expression by training; their advice today is to inhibit all expression, to practice a "poker face" in order to make the two sides of the face match in appearance. The outlook is equally dim for restoration of coordination in cases of severe nerve injury in other parts of the body.

This changed viewpoint reflects a revision in the picture of the entire nervous system. According to the new picture, the connections necessary for normal coordination arise in embryonic development according to a biochemically determined plan that precisely connects the various nerve endings in the body to their corresponding points in the nerve centers of the brain and spinal cord. Although the higher centers in the brain are capable of extensive learning, the lower centers in the brain stem and spinal cord are quite implastic. Because their function is dictated by their structure, it cannot be significantly modified by use or learning. Nor can the disordered connections set up by the random regeneration of injured nerves be corrected by re-education.

The evidence for this view, which comes from new experiments and from exacting clinical observations, is so persuasive that it is difficult to understand how the opposite view could have prevailed so long. It appears that most of the earlier reports of the high functional plasticity of the nervous system will go down in the record as unfortunate examples of how an erroneous medical or scientific opinion, once implanted, can snowball until it biases experimental observations and crushes dissenting interpretations.

Hundreds of experiments seemed to support the now-discounted opinion. One of the experiments most frequently cited was first reported in 1912 and was repeated with concurring interpretation as recently as 1941. In several monkeys opposing pairs of eye muscles were interchanged to reverse the movement of one eye. Upon recovery from surgery, the movements of the abnormally connected eye were said to coordinate with those of the normal one. In another oft-repeated experiment the nerves that control the lifting of the foot were crossed. Instead of a reversal of foot action, the animals showed recovery of muscle coordination hardly distinguishable from that on the normal side. Even when nerves from the forelimb were cross-connected to nerves of the hindlimb, the animals appeared to make complete

CROSSED SENSORY NERVES produce incorrect postural reflexes in the frog. The normal connections shown in the cross section of the spinal cord at top left cause the frog to withdraw an extended leg (*top center*) and to extend a flexed leg (*top right*) when a stimulus (*colored pointer*) is applied. If the sensory root entering the right side of the spinal cord is cut and surgically attached to the left side, as shown in the cross section at bottom left, the reactions of the left leg will be determined by the posture of the right.

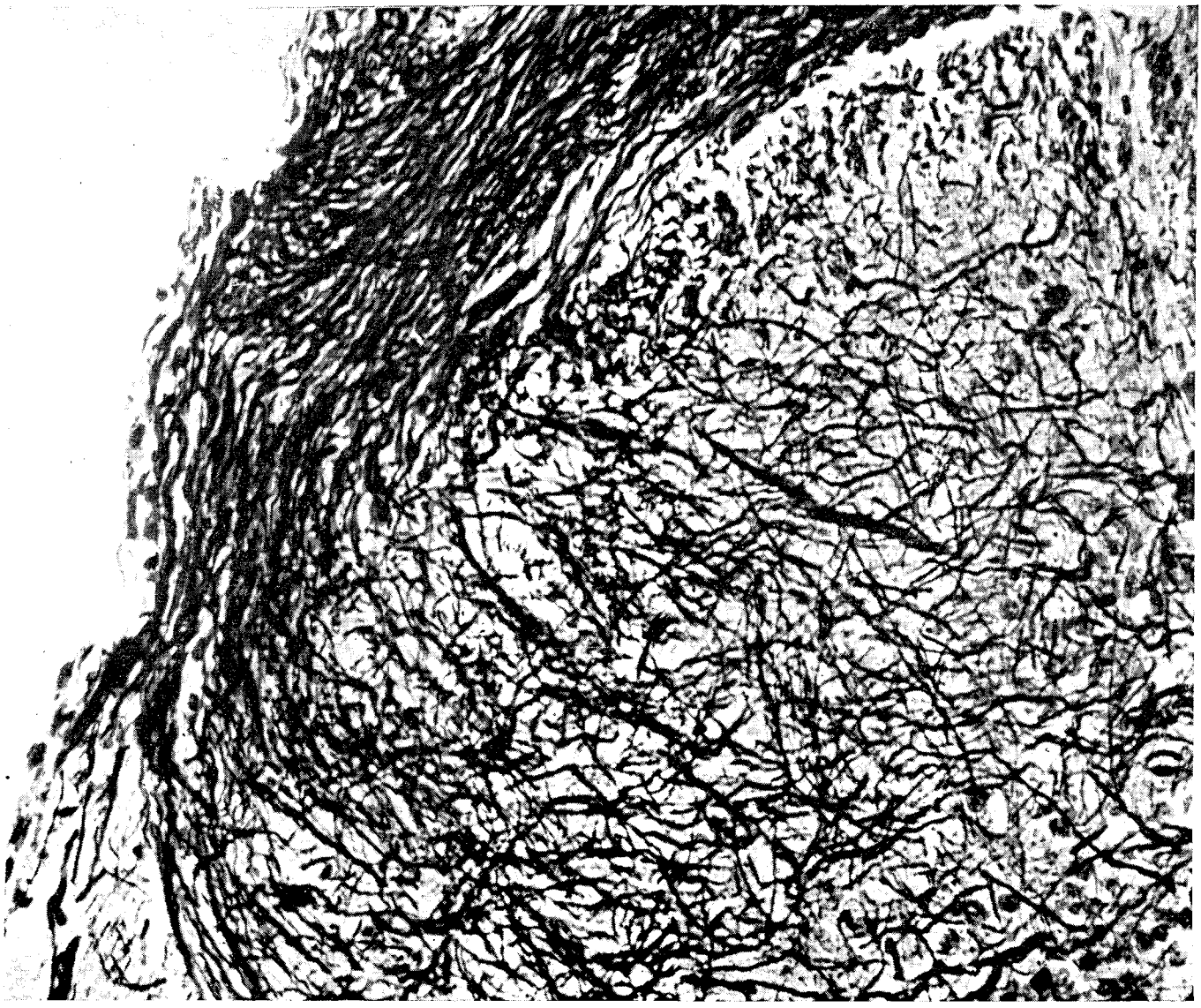
functional readjustment. With such results in the literature there seemed to be few limits to the restorative possibilities of peripheral nerve surgery.

The doctrine of the functional plasticity of the nervous system was sharply challenged in 1938 by Frank R. Ford and Barnes Woodhall of the Johns Hopkins School of Medicine. In an account of their clinical experience with functional disorders following the regeneration of nerves, they declared that these disorders persisted stubbornly in many of their patients for years without improvement. Their report cast serious doubt upon the accepted methods of therapy and the theory that rationalized them.

That same year I began a series of experiments in the laboratory of Paul Weiss at the University of Chicago. The initial aim of this investigation was to find out if functional plasticity was a property of the higher brain-centers only or whether it extended to the lowest levels of the spinal cord as alleged in some earlier reports. To explore the question I started to experiment on the simple reflexes involved in coordinating the foot movements of the rat. These reflexes depend upon a relatively simple circuit called a reflex arc. The fibers that activate the muscle connect to an association neuron in the spinal-reflex center: the association neuron is connected in turn to a particular type of sensory cell, the proprioceptive neuron, the terminal fibers of which are embedded in the muscle. This circuit, with the sensory nerve indicating the state of contraction or relaxation of the muscle and its orientation in space, provides the feedback necessary for proper muscle timing and coordination.

I switched the nerve connections between opposing muscles in the hindlimb of rats in such a way as to reverse the movement at the ankle joint. The nerves were cut, crossed and reunited end-to-end within tubes of dissected rat artery. Now whenever a nerve is severed, all fibers beyond the break degenerate and are absorbed. Even when they are united with the mechanical aid of an arterial tube, cut nerves do not heal together directly. New fibers sprout from the end of the central stump and grow into the muscles within the degenerate framework of the old nerve. After the surgery, I assumed, new coordinating circuits would be established and functional adjustment would follow quickly.

Much to my surprise the anticipated adjustment never occurred. The rats seemed unable to correct the reversals of motor coordination produced by the operation. When they tried to lift the



**POST-MORTEM VIEW of the frog's crossed sensory root (magnified 500 diameters) shows that the cut nerve-fibers have regenerated into the spinal cord. Despite their tangled appearance, the fibers have formed the connections necessary for proper muscle timing and coordination. Because the nerves have been transposed, however, frogs display abnormal reflexes shown on preceding page.**

affected foot, it pulled downward; when they tried to rise on the ball of the foot, their toes swung up and they fell back on their heels [*see illustration on next page*].

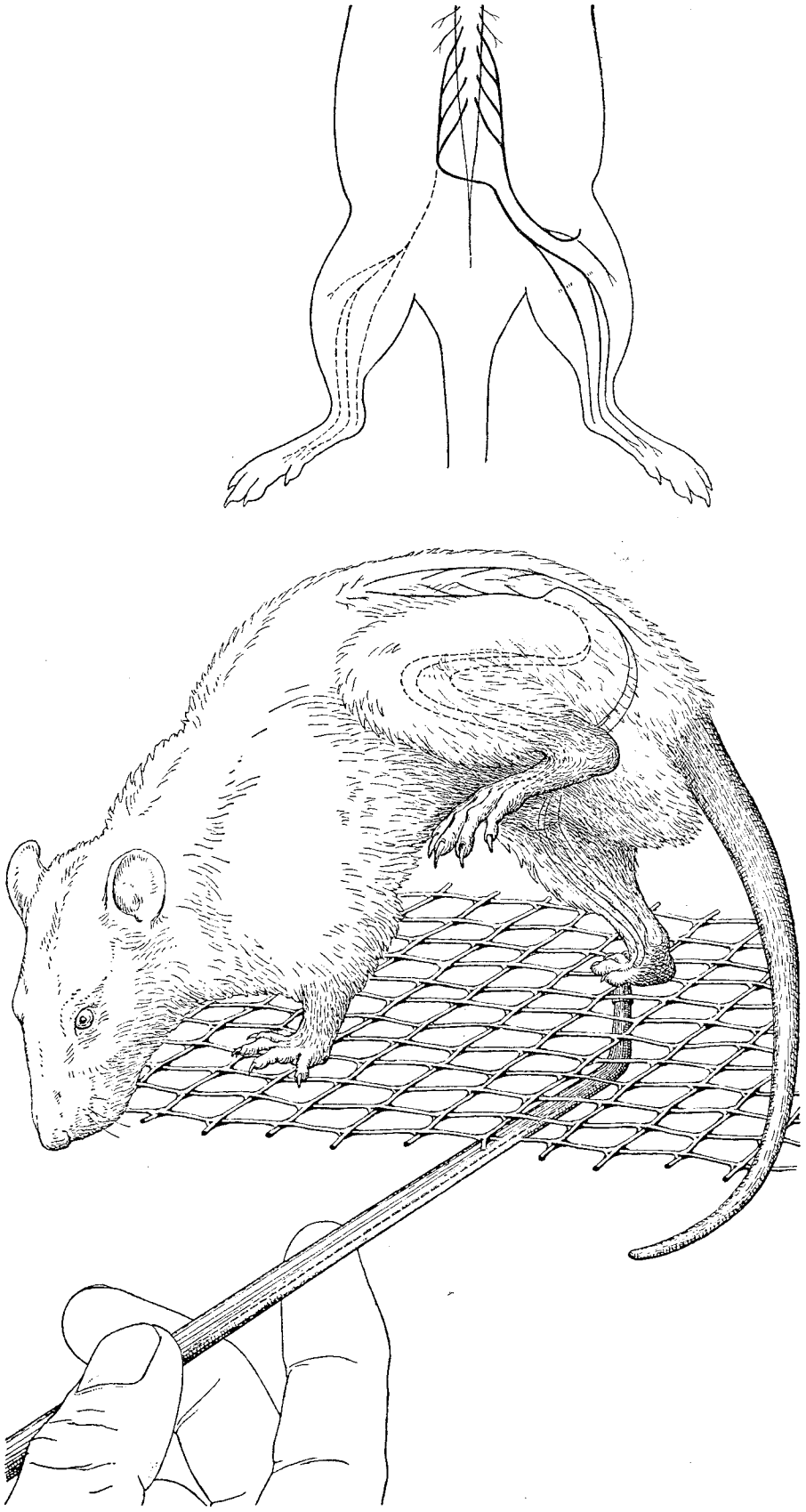
In a parallel experiment I presented the rats with a simpler readjustment problem by switching muscles instead of nerves. The muscles involved were transposed by cutting and crossing their tendons. Strong muscle-action was restored within two or three weeks. Yet the rats were still unable to correct the reversal of ankle movement. To check the experiment I tried crossing both muscles and nerves in a control group. Here the two reversals mutually canceled their effects, and the rat was able to raise and lower the foot in proper timing.

The rats with reversed foot-movements were put on a program of special training: they were forced to climb ladders and stretch upward on their hindlegs many times a day to get food pellets from automatic feeders. Yet the affected feet continued to work backward in machine-like fashion. We carried out a similar series of experiments on the forelimb, in which voluntary movements are under better control. But the rats still could not adapt to the rearrangement of the nerve connections.

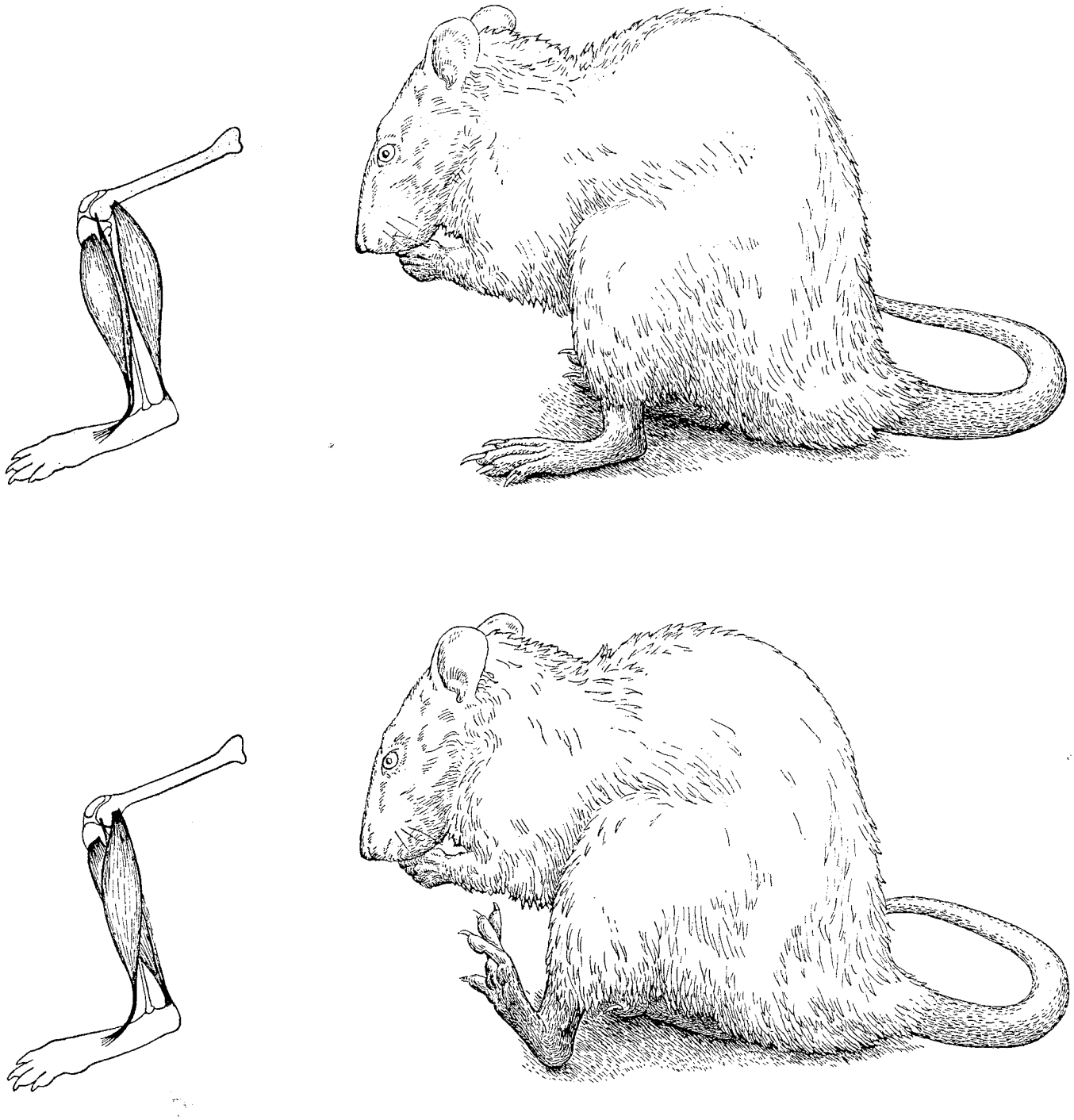
When it became clear that re-education had little or no effect in the rat's motor system, we turned to the sensory system. In the laboratory of Karl S. Lashley at Harvard University I transposed the nerves connecting to the skin of the left and right hindfeet [*see illustration at right*]. As the crossed hindlimb nerves regenerated, the rats began to exhibit false reference of sensations. In response to a mild electric shock to the sole of the right foot, the animals withdrew their left foot. This movement shifted their weight to the right foot, thereby increasing its contact with the offending electrode.

During the course of these experiments several rats developed a persistent sore on the sole of the right foot. Until the sores responded to medication, the animals hopped about on three feet with the fourth raised protectively—but it was always the wrong, uninjured foot that they raised. When they were prompted to lick the injury, they repeatedly licked the uninjured foot. Although this accidental soreness in the re-innervated foot presented the best kind of training situation, the rats still were unable to readapt.

Having concluded that it would be



INCORRECT WITHDRAWAL REFLEX and referred sensations appear in the rat after two sensory nerves are crossed. Here the main trunk-nerve to the left foot (*broken line*) has been crossed and connected to the corresponding nerve on the right side (*colored solid line*). Afterward, when sole of right foot is stimulated electrically, rat withdraws its left foot; if the shock is strong enough to produce soreness, rat licks its uninjured foot.



CROSSED MUSCLES produce the same effects as crossed nerves. In a normal rat (*top right*) the leg muscles are connected as shown at top left. When these connections are transposed (*bottom left*), the posture and movements of the ankle joint are reversed (*bottom right*). When the rat attempts to lift the affected foot, it pulls downward; when the animal tries to rise on the ball of the foot, the toes swing up and it falls back on its heels. Even with prolonged training, the rat can never learn to correct these movements.

difficult or impossible to demonstrate any sort of plasticity in the rat, we began a similar experiment on monkeys at the Yerkes Laboratories of Primate Biology in Orange Park, Fla. At first the monkeys seemed to make more progress than the rats: After we had transposed the nerves of the biceps and triceps muscles of the upper arm, they were quick to notice and to halt the reversed arm-movements that began to appear as the nerves regenerated. Thereafter the monkeys did attain a minor degree of readjustment in arm movement under the most simplified training routine. But after three years of testing and observation, they too failed to achieve any generalized positive correction in the action of the cross-innervated muscles.

The marked conflict between our results and those previously reported prompted us to reproduce the procedures of the earlier studies more closely. Instead of crossing isolated branch-nerves to single muscles I now crossed large trunk-nerves carrying motor impulses to many different muscles. All the muscles in the region were left intact and the nerves were permitted to regenerate into their respective areas at random.

In the hindlimb of the rat this operation produced neither a reversal of movement nor good functional readjustment; instead it caused a spastic con-

traction of all the muscles of the lower leg. Because of the greater strength of the postural or antigravity muscles, the contraction produced a stiltlike stiffening of the ankle joint in the extended position. This result was highly illuminating. Although the extended leg-posture was clearly abnormal in the rat, it could very easily be mistaken for a return of normal coordination in an animal that walks on its toes, like a dog or a cat. The fact that dogs and cats had been used in most of the earlier investigations made it apparent that nearly all of the hundreds of earlier reports of good functional recovery were subject to reinterpretation.

We know that central nervous system plasticity can be substantiated to some extent in cases where muscles have been transplanted in human patients. But even here we must make a distinction between the degree of plasticity demonstrated after muscle transposition and that shown after nerve regeneration. When a muscle is transplanted with its nerves intact, the motor cells that activate it continue to work together as a unit. On the other hand, in human beings and higher animals the fibers of a regenerating motor-nerve become haphazardly redistributed among the muscles it previously supplied. To restore these muscles to their previous control and coordination the reflex connections in the spinal cord would have to be reestablished down to the level of individual nerve cells. Even man's superb nervous system does not possess this degree of plasticity.

In most cases humans can learn to control transplanted muscles only in simple, slow, voluntary movements. The control of complex, rapid and reflex movements is limited at best, and is subject to relapse under conditions of fatigue, shock or surprise. Humans seem to have a much greater capacity for adjustment than the subhuman primates. Such re-education as does occur must therefore be due to the greater development of higher learning-centers in the human brain. Contrary to earlier supposition it does not reflect an intrinsic plasticity of nerve networks in general.

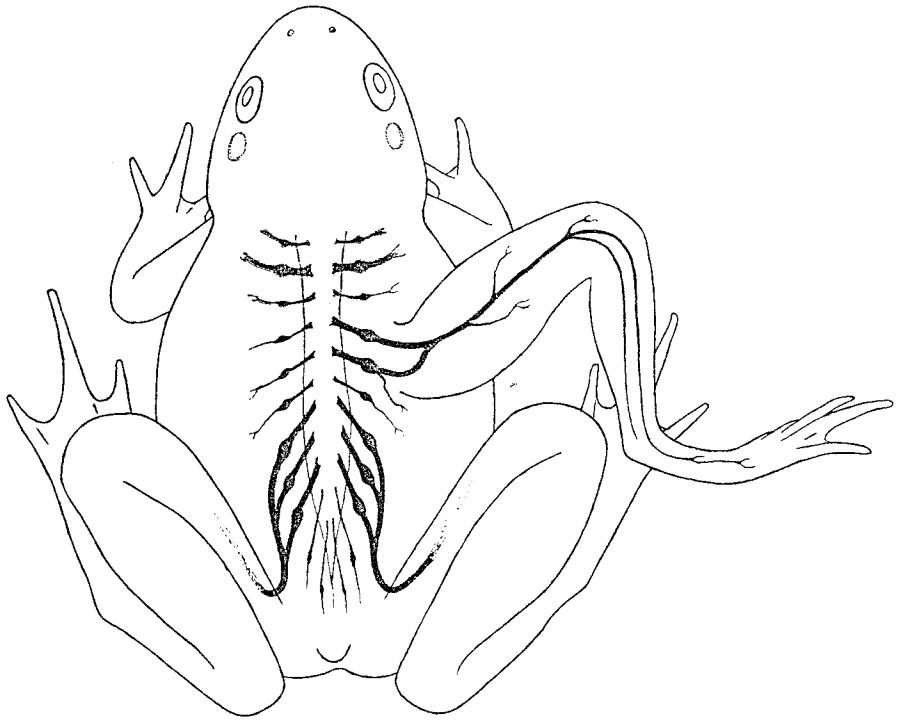
The nervous systems of reptiles, birds, and mammals other than primates show even less functional plasticity than those of primates. Farther down the evolutionary scale in the lower vertebrates, however, we find an entirely different type of neural plasticity: a structural plasticity not possessed by higher animals. Fishes, frogs and salamanders can regenerate any part of the central nervous system—even the tissue of the brain itself. Furthermore, if one of the large motor nerves of a salamander or a fish is cut, the animals re-establish normal reflex-arcs and recover coordination. This occurs even if several nerve stumps in a limb or fin are deliberately cross-connected to produce gross abnormalities in the distribution of the regenerating fibers.

In his pioneering investigations during the 1920's Paul Weiss was able to rule out the possibility that these spectacular recoveries could be based on learning or any other sort of functional plasticity. He transposed the developing forelimb buds of salamander embryos and reimplanted them with their front-to-back axes reversed. When function later appeared, the motor coordination in the transplanted limbs was perfectly normal, indicating that normal reflex-arcs had been established. Because the forelimbs were reversed in orientation, however, they pushed the animal backward when it tried to go forward, and vice versa. The perfectly coordinated reversed action persisted indefinitely without correction.

I was able to confirm the absence of any appreciable functional plasticity in amphibians in a set of experiments on the visual system of frogs and salamanders. In some I inverted the eyeballs surgically, producing upside-down vision; in others I cross-connected the eyes to the wrong sides of the brain, producing vision that was reversed from side to side. The animals never learned to correct the erroneous responses caused by this surgical rearrangement of their eyes [see "The Eye and the Brain," by R. W. Sperry; SCIENTIFIC AMERICAN, May, 1956]. Even when the eyes of frog and salamander embryos were rotated prior to the onset of vision (in later experiments by L. S. Stone at Yale University and George Szekely in Hungary), the same visual disorientation developed and persisted throughout life.

The evidence at present thus indicates that the structural plasticity observed in lower vertebrates is inherent in the growth process and is quite independent of function. It is as if the forces of embryonic development that laid down the circuits in the beginning continue to operate in regeneration. We have as yet only preliminary insight into the nature of these forces.

In studies now in progress at the California Institute of Technology Harbans Arora has made an interesting observation on the regeneration of the nerve controlling the eye muscle in fishes. His findings suggest that fibers directed by chance to their own muscles make connections more readily than foreign fibers reaching the same muscle. As a result the fibers that originally con-



ABNORMAL REFLEX ARCS develop when a hindlimb bud is grafted onto the back of a tadpole. As the tadpole grows, sensory nerves destined for the skin of the back, flank and belly invade the nerveless extra limb and form spinal connections appropriate for limb reflexes. When grafted limb is stimulated in adult frog, muscles of the right hindlimb respond.

trolled the muscle tend to recapture control in regeneration. Such selective reaffiliation of nerve and muscle indicates that some chemical specificity must match one to the other.

Selective outgrowth of regenerating nerves to their proper end-organs seems not to be the rule, however, even in lower forms. Among mammals it has not been found at all, except on the much more gross scale that differentiates sensory from motor endings, smooth muscle from striated muscle, muscle from gland, and so on. Nor does simple selective outgrowth account for the restoration of function in salamanders. The early studies by Weiss showed that fiber outgrowth and muscle re-innervation generally proceed in these animals in a random, nonselective manner, comparable to that in mammals. Upon re-innervation, however, salamander muscles regain their former coordination and timing, even when their function is disoriented by nerve-crossing.

These observations suggest that the rearrangement of connections in the periphery of the salamander nervous system has chemical repercussions that result in a compensatory shift of reflex relations at the centers. It is postulated that the motor-nerve cells regenerating into new muscles take on a new chemical flavor, as it were. Thereupon their old central associations dissolve, and new ones form to match the new terminals in the periphery. The reflex circuit would thus be restored to its original state, with the peripheral and central terminals linked by a new pathway. Higher animals, lacking this embryonic type of structural plasticity, show no restoration of function.

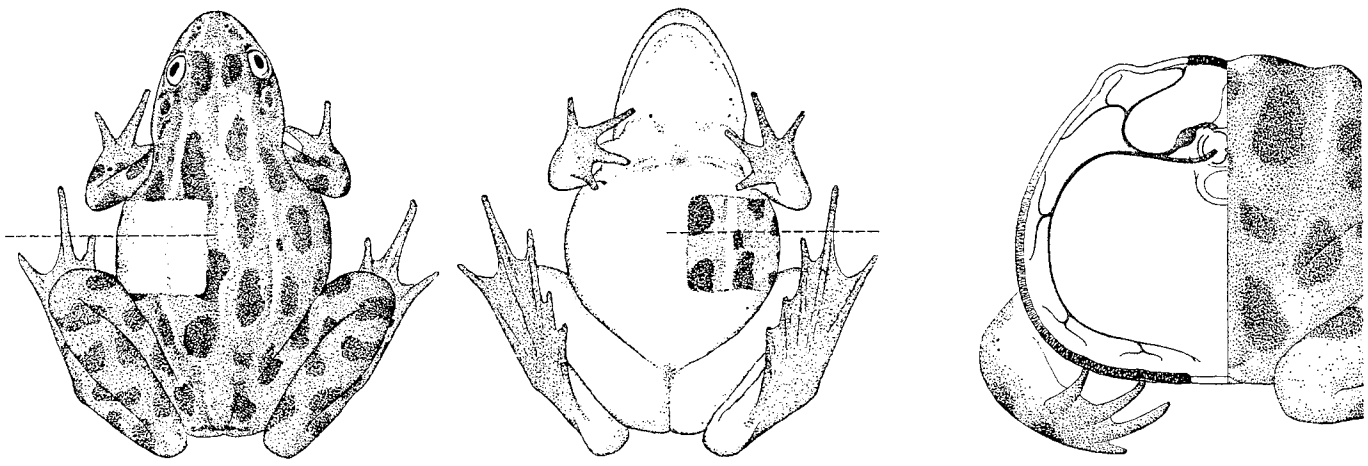
This explanation at first seemed rather far-fetched, especially from the standpoint of electrophysiology, which offers no evidence for such qualitative specificity among nerve fibers. However, the underlying idea is well supported by recent experiments on the regeneration of sensory nerves.

At the University of Chicago Nancy M. Miner, one of my former associates, is responsible for a significant series of experiments indicating the role of some sort of chemical specificity in the hookup of the nervous system. She grafted extra hindlimb buds onto the backs of tadpoles; the buds became connected to the sensory fibers that would normally innervate the skin of the belly, flank and back [*see illustration on preceding page*]. The grafted leg served only as a sensory field for the nearby sensory nerves because there are no nearby limb nerves to invade it. When a stimulus was applied to the grafted limb in the mature frog, the animal moved the normal hindlimb on the same side, just as it would if the normal limb had received the stimulus. The belly and trunk nerves connected to the grafted limb had evidently taken on a hindlimb "flavor" and then formed the appropriate reflex connections in the central nervous system. In another experiment Miner removed a strip of skin from the trunk of a tadpole, cut its nerves and replaced it so that the skin of the back now covered the belly, and vice versa [*see illustration below*]. When the grown frogs were stimulated in the grafted area of the back, they responded by wiping at the belly with the forelimb; when they were stimulated in the grafted area on the belly, they wiped at the back with the hindlimb.

To account for these experimental findings it is necessary to conclude that the sensory fibers that made connections to the grafted tissues must have been modified by the character of these tissues. It is therefore unnecessary to postulate that each nerve fiber in embryonic development makes some predestined contact with a particular terminal point in the skin. Growing freely into the nearest area not yet innervated, the fibers establish their peripheral terminals at random. Thereafter they must proceed to form central hookups appropriate for the particular kind of skin to which they have become attached. It seems clearly to be some quality in the skin at the outer end of the circuit that determines the pattern of the reflex connections established at the center.

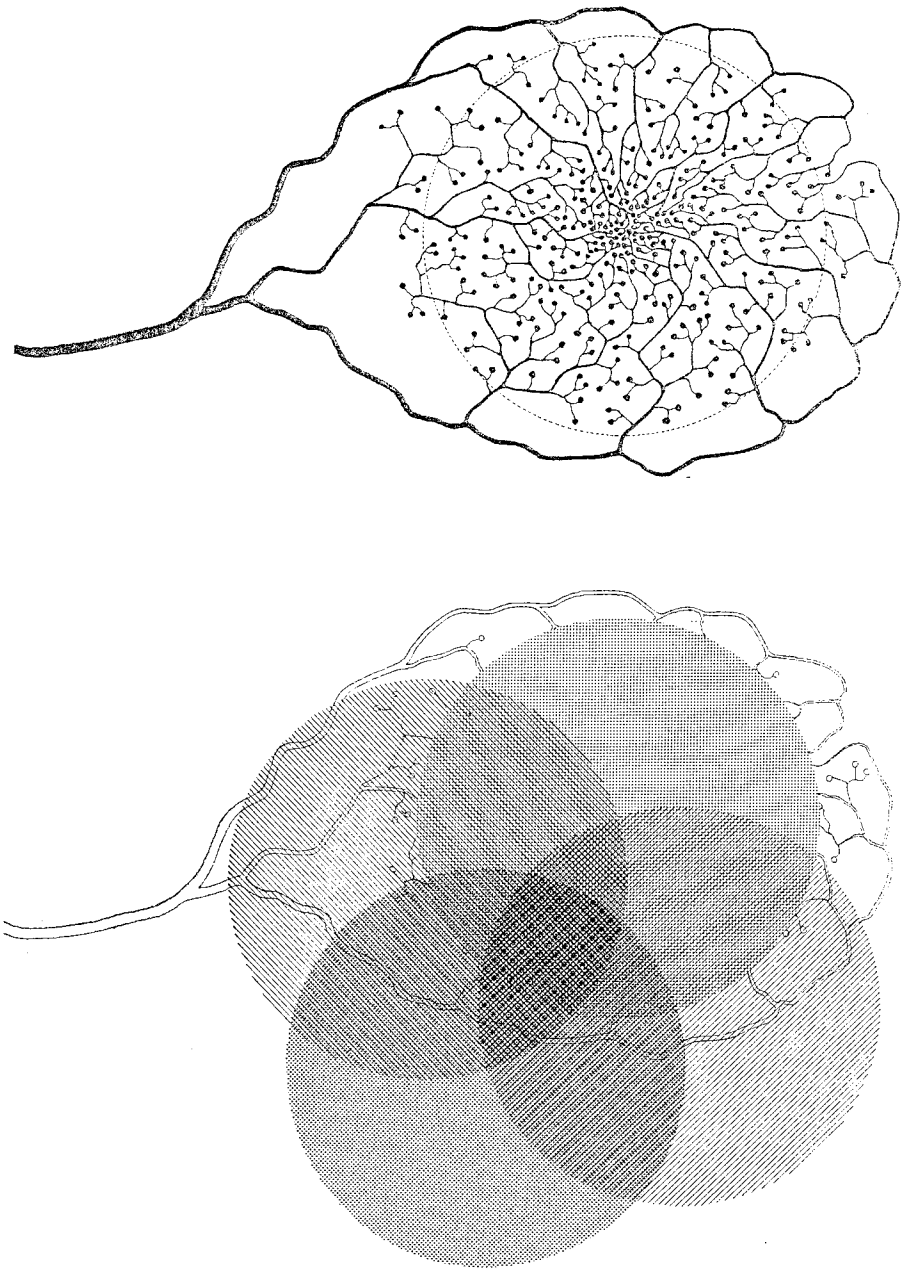
No attraction from a distance need be invoked in this selective patterning of the central hookup. The multiple branches of each nerve fiber undergo extensive ramification among the central nerve cells, with the tips of the branches making numerous contacts with all the cells in the vicinity. Presumably most of the contacts do not affect the growing fiber-tips. It is only when contact is made with central nerve cells which have the appropriate chemical specificity that the growing fiber adheres and forms the specialized synaptic ending capable of transmitting the nerve impulse.

In man these observations and interpretations provide the basis for the new



ROTATED PATCH OF SKIN demonstrates how embryonic nerves respond to the biochemical "flavor" of the tissues they innervate. Here a strip of skin was removed from a tadpole, cut free of all connections, and replaced so that the skin of the back now covered the belly and vice versa. In the grown frog the skin retained its original color and flavor despite its location, as shown in the dorsal and ventral views (*left and center, respectively*). The cutaway view at right (*made along broken lines*) shows how new nerves have invaded the graft and formed spinal reflex-arcs appropriate to the skin's flavor rather than to its location. Thus when the belly skin on the back is stimulated, the frog wipes at its belly; when the back graft on the belly is stimulated, the frog wipes at its back.

view of the nervous system which holds that its networks are determined by biochemical processes in the course of embryonic growth. Let us consider this scheme in connection with the extreme localization of skin sensations that makes it possible to locate a pinprick, for example, anywhere on the body surface. This "local sign" quality depends upon the precise matching between the central and peripheral connection of each one of thousands upon thousands of cutaneous nerve fibers connecting the skin surfaces to the spinal cord and brain. During embryonic growth we may assume that the skin undergoes a highly refined differentiation until each spot on the skin acquires a unique chemical make-up. A mosaic is not envisaged here but rather smooth gradients of differentiation extending from front to back and from top to bottom, with local elaborations of these basic gradients in the regions of the limbs. Each skin locus becomes distinguished by a given latitude and longitude, so to speak, expressed in the tissues as a combination of biochemical properties. The cutaneous nerves, as they grow out from their central ganglia, may terminate largely at random in their respective local areas. Through intimate terminal contacts the specific local flavor is imparted to each nerve fiber. This specificity is then transmitted along the fiber to all parts of the nerve cell including its ramification within the central nervous system. In this way the local-sign properties of the skin become stamped secondarily upon the cutaneous nerves and are carried into the sensory centers of the brain and spinal cord. Precise localization is further enhanced by the overlapping of the terminal connections formed by the fibers in the skin [*see illustration at right*].



**OVERLAP OF SENSORY FIBERS** permits a subject to localize a pinprick accurately. The schematic diagram at top shows the terminal branches of a single cutaneous fiber; the branches are most abundant at the center of the area they innervate (*broken circle*). Bottom diagram shows how this area overlaps those of three other fibers. As shading indicates, each of the areas transmits a recognizably different signal to the central nervous system.

Implicit in this theory is the assumption that in the embryo the cerebral cortex and the lower relay-centers also undergo a differentiation that parallels in miniature that of the body surface. In other words, just as from the skin to the first central connection point in the spinal cord, so from relay to relay and finally to the cortex the central linkages arise on the basis of selective chemical affinities. At each of its ascending levels the nervous system forms a maplike projection of the body surface.

This mechanism presumably operates not only in the sensory system but in the nervous system in general. Since the organization of the lower nerve centers and the peripheral nerve circuits in higher animals seems to take place only in the early plastic stages of growth, it is clear that injury to them later on cannot be repaired by any amount of re-education and training. In the structural plasticity of the system in lower animals, however, we are able to observe the processes by which our own nervous systems develop.

The new approach provides a sound biological basis for the explanation of built-in behavior mechanisms generally, from the simplest reflexes to the most complicated patterns of inherited behavior. It brings the study of behavior into the realm of experimental embryology on the same basis as other organs and organ systems. Although learning must now yield its former monopolistic status, we must not infer that it has no role in brain development. Particularly in man, whose brain grows and matures for many years, learning is a powerful method of imposing additional organization on the higher levels of the nervous system. Until the neural basis of learning is discovered, however, we cannot say whether it produces this added organization by changing the actual layout and hookups of cerebral networks or simply by increasing the conductance of certain pre-established pathways.

# POISONS

What is the molecular mechanism by which a toxic substance produces its effect? In seeking the answer for various poisons, investigators have found invaluable tools for the study of normal cell physiology

by Elijah Adams

"Poisons can be employed as agents of life's destruction or as means for relief of disease, but in addition to these universally recognized uses there is a third that particularly interests the physiologist. For him the poison becomes an instrument that dissociates and analyzes the most delicate phenomena of the living machine, and by studying attentively the mechanism of death in diverse types of poisoning he can learn indirectly much about the physiological processes of life."

After almost a century these words of the eminent French physiologist Claude Bernard still summarize concisely the scientific significance of poisons. Curare, the specific agent that he was discussing, remains one of the best examples of the tripartite nature of this loose category of substances. When curare first came to Bernard's attention, Europeans knew it only as an arrow poison used by Indians in South America to kill game and enemies. Bernard himself first applied it as a physiological scalpel in his pioneering studies of nerve and muscle function. More recently curare has become a "means for the relief of disease": as an adjunct to surgery it relaxes the muscles and thereby obviates dangerously deep levels of anesthesia.

A poison is difficult to define with legalistic rigor. Even distilled water is toxic when it is consumed by the gallon, and considerably smaller quantities of water can cause death when they are inhaled. The accepted pharmacological definition follows popular usage: A poison is any substance that in relatively small quantities can cause death or illness in living organisms by chemical action. The last clause rules out such mechanically lethal effects as those produced by a small quantity of lead entering the body at high velocity.

The list of poisons furnished readymade by nature has been extended mightily in recent years by human ingenuity and the chemical industry. No reasonable definition of poisons can exclude the thousands of substances which in small doses produce physiological changes but which, being used customarily for the treatment of disease, are identified as drugs. Another deceptive category is that of the pesticides, especially those designed to kill our close physiological relatives the rodents. It is not surprising that poisons represent a major public hazard, particularly to children. In 1955 about 8,000 Americans died of poisons (exclusive of ethyl alcohol). The fatalities were about equally divided between accidents and suicides; homicides accounted for only .5 per cent of the total. Non-fatal poisonings are estimated at a million or more per year, about 25 per cent of them in children under five.

The term "poison" (akin to "potion") originally included medicinal as well as lethal draughts. For example, digitoxin —the medication of choice in certain cardiac conditions—is among the most toxic substances known; its use as an industrial chemical would necessitate elaborate safety precautions. Courses in pharmacology properly emphasize the broad overlap between drugs and poisons, and physicians, nurses and pharmacists dare not forget it.

To the physiologist, on the other hand, poisons are no more interesting than any other physiologically active compound. Like all such substances, they challenge him to interpret their gross effects in molecular terms—to elucidate the chemical mechanisms by which they derange or destroy cells and thereby induce more obvious disturbances of the entire organism. So far the attempt to reduce toxicity to molecular mechanisms has succeeded in only a few cases. As Bernard anticipated, however, it has meanwhile taught us a good deal about the chemistry of living matter.

The corrosive poisons—strong acids and alkalis—have the most obvious effects. At first glance their mode of action seems simple enough. By massive destruction of cells they can produce death from shock, hemorrhage or incapacitation of some vital organ. Thus the corrosive gas phosgene, used in chemical warfare during World War I, reacts with water in the lungs to produce hydrochloric acid. This destroys lung tissue and by its irritant action fills the lungs with fluid. Death ultimately results from asphyxiation. With most corrosive poisons, however, the mode of action is not so clearly discernible. Concentrated sulfuric acid, for example, does so many things to the body that its specifically lethal activities are hard to isolate. Moreover, its catastrophic effects on tissue leave little for the physiologist to examine. Some corrosive poisons may produce death simply by shifting the delicate acid-alkaline balance of the body to the point where vital chemical reactions can no longer occur.

More subtle in their effects are the metabolic poisons, a group that includes most of the drugs in the pharmacopoeia as well as many other substances that have no place in medicine. These compounds do not destroy tissues; many of them produce no visible tissue-change whatever. Instead they accomplish their lethal work by disrupting one or another of the intricate chemical reactions upon which life depends.

The effects of two common metabolic poisons were explained many years ago